Stronger Brønsted Acids

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Takahiko Akiyama was born in 1958 in Kurashiki, Japan. He received his Ph.D. degree in 1985 from the University of Tokyo under the direction of Professor T. Mukaiyama. Immediately thereafter he joined Shionogi Research Laboratories (Osaka, Japan) as a research chemist. In 1988 he was appointed Assistant Professor at Ehime University. He joined Professor B. M. Trost's group at Stanford University in 1992 as a visiting scholar. He was appointed Associate Professor at Gakushuin University in 1994. Since 1997 he has been Full Professor at Gakushuin University. His research interests center around development of novel synthetic methods in particular focused on asymmetric synthesis using organocatalysts as well as metal catalysts.

1. Introduction

The fundamental role of the Lewis-acid catalyst lies in the activation of the C═X bond (X = O, NR, CR_2), thereby decreasing the LUMO energy and promoting nucleophilic addition to the C═X bond. A number of metal-centered Lewis-acid catalysts have been developed for that purpose.[1] The combination of a Lewis acid and a chiral ligand results in the in situ formation of a chiral Lewis-acid catalyst. Chiral Lewis-acid catalysts have been investigated extensively, and excellent enantioselectivity has been realized.[2]

The proton is the smallest element of the Lewis acid. While Lewis-acid catalysts have been widely employed as catalysts for carbon−carbon bond-forming reactions, Brønsted acids have been employed mainly as catalysts for hydrolysis and/or formation of esters, acetals, etc. (Figure 1). The synthetic utility of a Brønsted acid as a catalyst for carbon−carbon bond-forming reactions has been quite limited until recently. Chiral Brønsted-acid catalysts[3] have recently emerged as a new class of organocatalysts[4] for a number of enantioselective carbon−carbon bond-forming reactions.

In contrast to the Lewis acids, Brønsted acids are easy to handle and generally stable toward oxygen and water and can be stored for a long period of time. From a practical point of view, organocatalysts should be environmentally friendly and applicable to large-scale synthesis. With respect to asymmetric catalysts, these features are more prominent. Chiral Lewis-acid catalyst is, in principle, prepared from Lewis acid and chiral ligand in situ and employed immediately after preparation. In contrast, chiral Brønsted acid, being a small organic molecule, exhibits catalytic activity as it is.

Chiral Brønsted acids are classified into two categories: (1) neutral Brønsted acids, such as thiourea[5] and TADDOL[6] derivatives, which are called hydrogen-bonding catalysts, and (2) stronger Brønsted acids, such as BINOL derivatives and phosphoric acids (Figure 2). We will focus on stronger Brønsted-acid catalysts in this review.

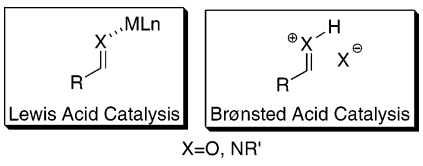

Figure 1. Lewis-acid catalysis and Brønsted-acid catalysis.

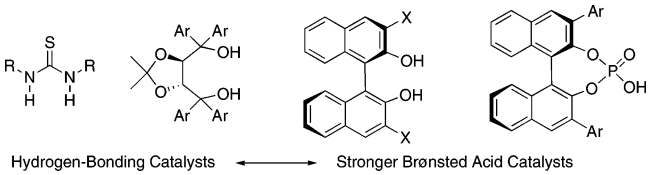

Figure 2. Chiral Brønsted acids.

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Although excellent results have been reported for enantioselective protonation by means of chiral Brønsted acids, this topic will not be included here.[7]

Before discussing the enantioselective reactions catalyzed by chiral Brønsted acids, we will briefly survey some important carbon−carbon bond-forming reactions catalyzed by achiral Brønsted acids (Figure 3).

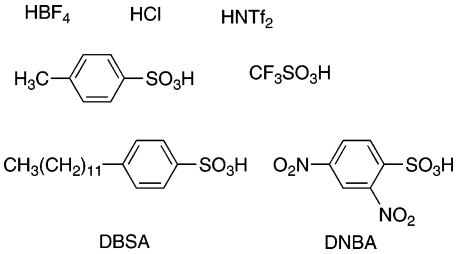


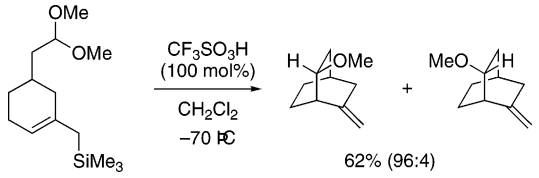
Figure 3. Examples of achiral Brønsted acids.

2. Achiral Brønsted Acids

2.1. Reactions with Carbonyl Compounds

Denmark and co-workers examined a range of Lewis acids during the investigation of the reaction mechanism and stereochemical course of the intramolecular addition of allylsilane to acetal. A stoichiometric amount of trifluoromethanesulfonic acid was effective as a Brønsted-acid catalyst in addition to the conventional Lewis acids, such as $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, and TMSOTf (Scheme 1).[8]

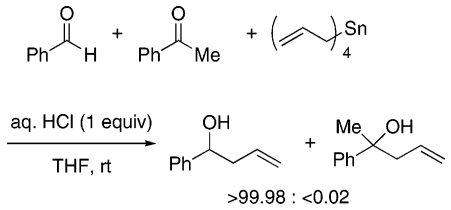
Scheme 1



Denmark,[9] Keck,[10] and Yamamoto[11] studied the intramolecular allylation reaction of aldehyde with allylstannane by means of Brønsted acids such as CF_3SO_3H, CF_3CO_2H, and CCl_3CO_2H.[12]

The intermolecular addition of allylic metal to aldehyde was reported by Yamamoto and Yanagisawa (Scheme 2),[13]

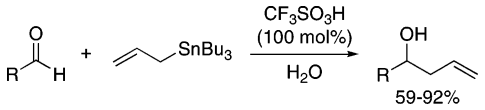
Scheme 2



who employed aq. HCl to promote the allylation of tetraallylstannane to aldehyde in aqueous THF. The allylation reactions exhibited high chemoselectivity toward aldehyde rather than ketone.

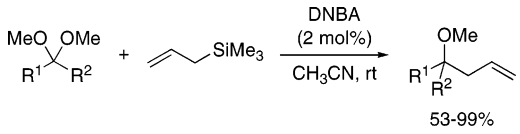
Loh and co-workers reported the allylation of aldehyde with tributylstannane promoted by trifluoromethanesulfonic acid in water (Scheme 3).[14]

Scheme 3



Recently, List and co-worker reported that 2,4-dinitrobenzenesulfonic acid (DNBA) catalyzed the Hosomi−Sakurai reaction of allylsilane with acetals (Scheme 4).[15] The

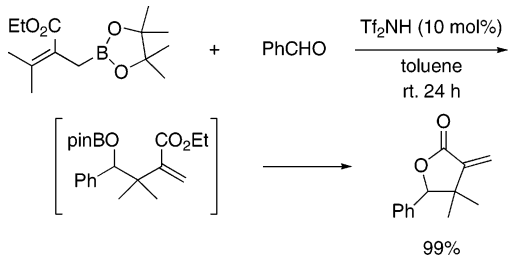
Scheme 4



corresponding homoallylic ethers were obtained in high yields despite the small catalyst load.

Hall and co-workers reported that allylboronates underwent allylboration by means of TfOH, and subsequent cyclization gave α-exo-methylene-γ-lactones in good yields (Scheme 5).[16] This novel procedure was applied to the synthesis of

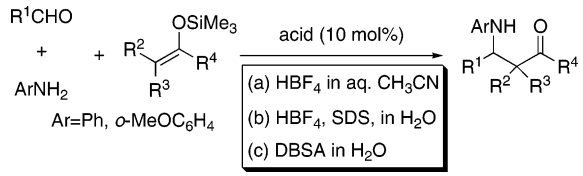
Scheme 5



all four diastereomers of eupomatilone-6, a member of a structurally intriguing class of lignans.

Our group has reported that HBF_4 is an efficient catalyst for the three-component Mannich-type reaction of aldehyde, aniline, and silyl enolates in aqueous organic solvent (Scheme 6).[17] The Mannich-type reaction proceeded smoothly in water

Scheme 6



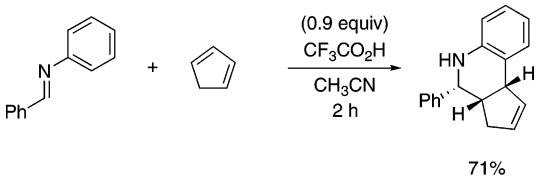
without organic solvent in the presence of sodium dodecyl sulfate (SDS) as a surfactant.[18] Kobayashi and co-workers found that dodecylbenzenesulfonic acid (DBSA) is an effective catalyst for the Mannich-type reaction in water.[19] They subsequently reported the three-component Mannich reaction in water,[20] which was catalyzed by hydrophobic polystyrene-supported sulfonic acid.[21]

Cai and co-workers found that camphorsulfonic acid is an efficient catalyst for the direct Mannich reaction of benzaldehyde, aniline, and various ketones in aqueous media to give β-amino esters with good diastereo- and regioselectivities.[22]

Several reports on the Brønsted-acid-catalyzed aza Diels−Alder reactions are available.[23] Grieco and co-worker reported the aza Diels−Alder reaction of cyclopentadiene with simple iminium salts in aqueous media.[24] We investigated the HBF_4-catalyzed aza Diels−Alder reaction of

aldimine, generated in situ, with Danishefsky's diene in aqueous media.[25] Grieco and co-worker reported the CF_3-CO_2H-catalyzed inverse electron-demand aza Diels−Alder reaction of *N*-aryl aldimine with cyclopentadiene to give a tetrahydroquinoline derivative (Scheme 7).[26] *p*-TsOH,[27] PPh_3-

Scheme 7



$HClO_4$,[28] and trifluoromethanesulfonic acid[29] catalyzed the aza Diels−Alder reaction of *N*-aryl aldimine with electron-rich alkene to furnish tetrahydroquinoline derivatives.

DBSA is also effective as a catalyst for the direct esterification of carboxylic acid with alcohols in an emulsion system.[30] Interestingly, dehydrative ester formation proceeded smoothly in water.

Perfluorinated resinsulfonic acids, such as Nafion-H and its modified derivatives, have been extensively employed as superacids in organic synthesis.[31] The trifluoromethylsulfonyl group is one of the strongest neutral electron-withdrawing groups.[32] For example, phenylbis(triflyl)methane (pK_a = 7.83 in CH_3CN)[33] is a strong non-oxidizing acid. Yamamoto and Ishihara designed pentafluorophenylbis(triflyl)methane **1** and polystyrene-bound tetrafluorophenylbis(triflyl)methane **2** as organic-solvent-swellable and strong Brønsted-acid catalysts (Figure 4).[34] Polymer-bound catalyst 2 was effective for a

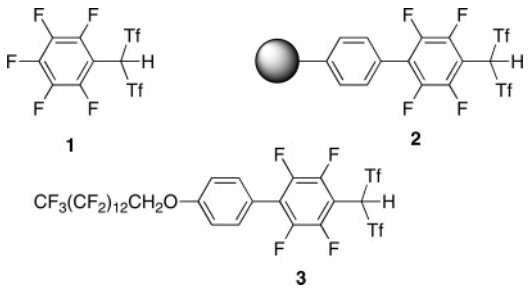
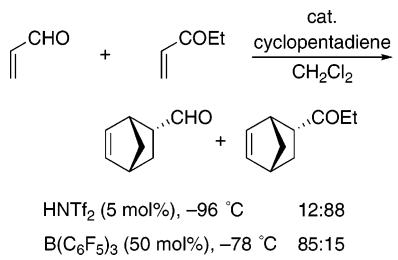


Figure 4. Perfluorinated acids.

number of synthetic transformations such as the Friedel−Crafts acylation, the Mukaiyama−aldol reaction, the Hosomi−Sakurai allylation of aldehyde, and acetalization. The activity of 2 is superior to that of Nafion-H because it can be effectively swollen in organic solvent. Furthermore, it can be recovered quantitatively and reused. The super Brønsted acid was employed as a single-pass reaction column.[35] The application of a fluorous catalyst 3 to a conventional solvent system has been reported.[36]

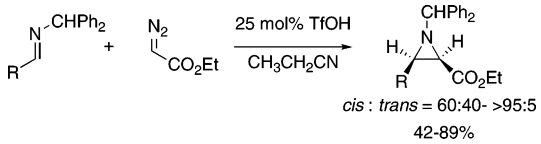
Bistrifluoromethanesulfonimide ($HNTf_2$) has been employed to catalyze Friedel−Crafts reactions, Mukaiyama aldol reactions, and C-glycosylation reactions.[37] Yamamoto and co-worker disclosed the reversal of chemoselectivity in the Diels−Alder reaction with α,β-unsaturated aldehydes and ketones catalyzed by Brønsted acid or Lewis acid (Scheme 8).[38] A proton, the smallest Lewis acid, selectively coordinates to a more basic carbonyl group such as α,β-unsaturated ketone. On the other hand, bulky Lewis acid, $B(C_6F_5)_3$, preferentially coordinates to α,β-unsaturated aldehyde due to the severe steric repulsion in α,β-unsaturated ketone.

Scheme 8



Johnston and co-workers reported the aza Darzens reaction catalyzed by trifluoromethanesulfonic acid (Scheme 9).[39]

Scheme 9



Aziridines were obtained in favor of the cis isomers, and no products resulting from acid-promoted aziridine ring opening were observed.

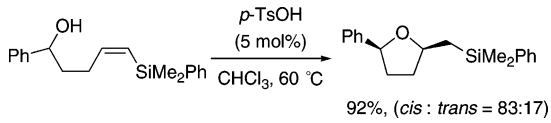
2.2. Reactions with Alkenes and Alkynes

Although the Brønsted-acid-mediated hydration of alkenes has been known for more than 50 years,[40] the acid-catalyzed addition of heteroatom or carbon nucleophile to simple alkenes has been underinvestigated until recently.

Brønsted-acid-catalyzed hydroxylation and hydroamination reactions have been reported by use of activated alkenes, such as allenylsilane and allylsilane.[41]

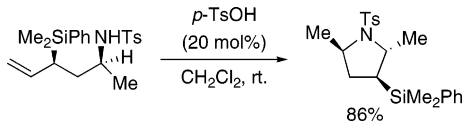
Hosomi and co-workers studied the cyclization of vinylsilane bearing a hydroxy or amino group catalyzed by *p*-TsOH as well as $TiCl_4$. Tetrahydrofuran[42] and pyrrolidine derivatives[43] were obtained stereoselectively (Scheme 10).[44]

Scheme 10



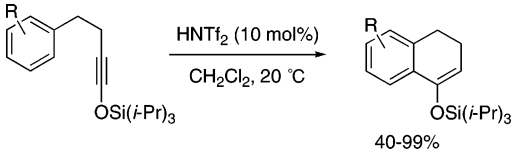
Brønsted-acid-catalyzed cyclization of allylsilane leading to tetrahydrofuran[45] and pyrrolidine[46] has been also reported (Scheme 11).

Scheme 11



Kozmin and co-worker reported the first Brønsted-acid-mediated carbocyclization of siloxyalkynes, which gave tetralone derivatives in good yields (Scheme 12).[47] They

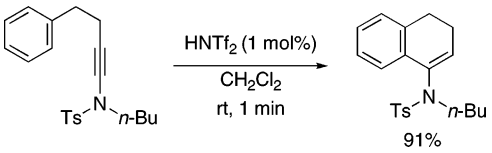
Scheme 12



investigated a number of metal catalysts, including Hg, Hf, Ga, Au, and Ag, and found that $HNTf_2$ is the catalyst of choice.

Hsung and co-workers reported highly stereoselective arene−ynamine cyclizations catalyzed by $HNTf_2$ (Scheme 13).[48] This reaction constitutes a keteniminium variant of

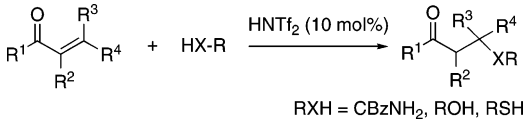
Scheme 13



Pictet−Spengler cyclizations, providing an efficient route for the synthesis of nitrogen heterocycles such as indoles.

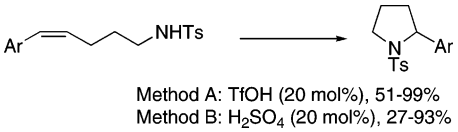
The Michael addition of nitrogen, oxygen, and sulfur nucleophiles to α,β-unsaturated ketone was effected by $HNTf_2$ (10 mol %) (Scheme 14).[49]

Scheme 14



Hartwig and co-worker reported the intramolecular hydroamination of protected alkenylamines by means of TfOH or H_2SO_4 in 2002 (Scheme 15).[50] Pyrrolidines and piperidines

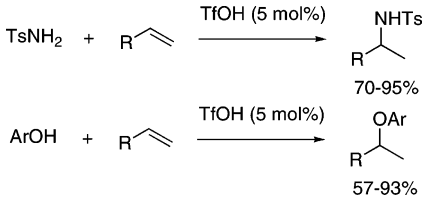
Scheme 15



were obtained in good yields. On the other hand, Bergman reported the $[PhNH_3][B(C_6F_5)_4]$-catalyzed hydroamination of activated alkenes with anilines.[51]

He[52] and Hartwig[53] independently reported the intermolecular addition of phenols, carboxylic acids, and tosylamides to unactivated alkenes catalyzed by TfOH (Scheme 16).[54] It

Scheme 16



is essential to employ a catalytic amount of TfOH. Increasing the catalyst load significantly reduced the yields of the addition products. The reactions between N−H and O−H bond donors and unactivated olefins so far catalyzed by metal triflates might be actually catalyzed by triflic acid.

3. Chiral Brønsted Acids

3.1. Lewis-Acid-Assisted Chiral Brønsted Acids

Before discussing the organo-based chiral Brønsted acids, metal-assisted designer chiral Brønsted acid will be introduced.

Yamamoto and Ishihara proposed the concept, "Lewis-acid-assisted chiral Brønsted acid," which involves a combination of chiral phenol derivative and Lewis acid.[55] A strong Brønsted acid is generated by the assistance of the coordinated Lewis acid (Figure 5). They employed chiral

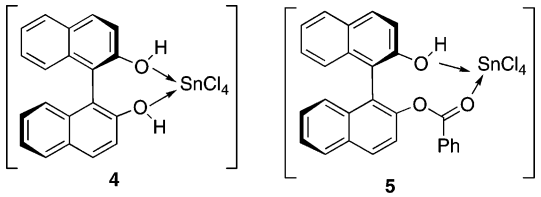
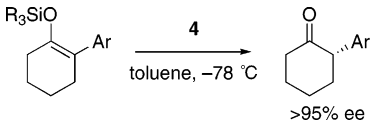


Figure 5. Lewis-acid-assisted chiral Brønsted acids.

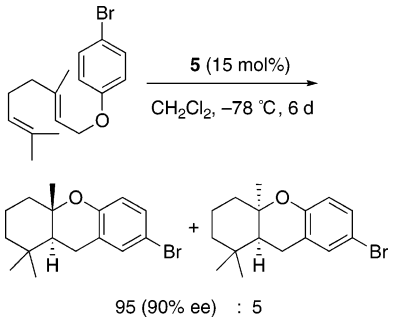
Brønsted acid 4, which was generated in situ from (*R*)-BINOL and $SnCl_4$, for the enantioselective protonation of silyl enol ethers (Scheme 17).[56]

Scheme 17



They extended the catalyst for the first biomimetic cyclization of polyprenoids by means of the Lewis-acid-assisted Brønsted acid (Scheme 18).[57]

Scheme 18

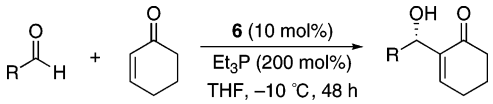


3.2. Binaphthol Derivatives

As weakly acidic chiral Brønsted acids, a number of BINOL catalysts have been developed recently (Figure 6).

Schaus and co-workers reported the enantioselective Morita−Baylis−Hillman[58] reaction that involved the use of BINOL derivative 6 in the presence of a stoichiometric amount of PEt_3 (Table 1).[59] A range of aliphatic aldehydes

Table 1. Morita−Baylis−Hillman Reaction



entry	R	yield (%)	ee (%)
1	$PhCH_2CH_2$	88	90
2	(*Z*)-$CH_3CH_2CH{=}CH(CH_2)_2$	72	96
3	*c*-C_6H_{11}	71	96
4	*i*-Pr	82	95
5	PhCH=CH	39	81

worked well to furnish the corresponding adducts with high to excellent enantioselectivities.

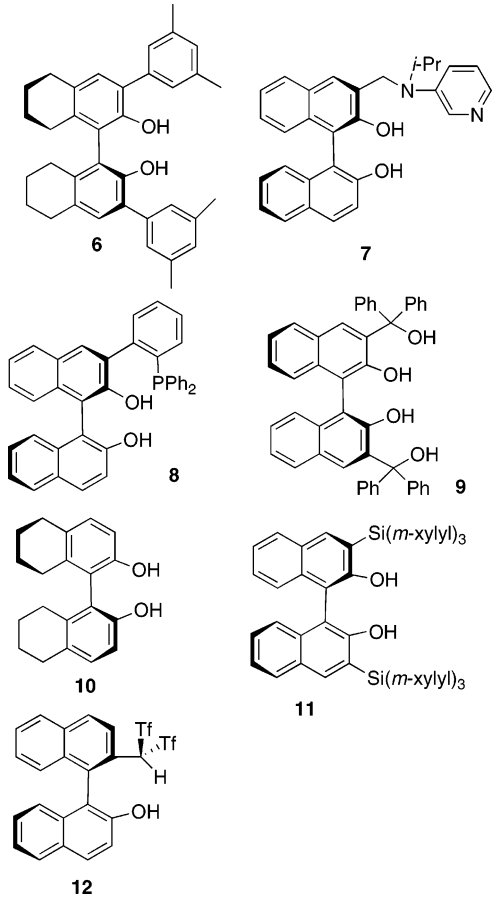
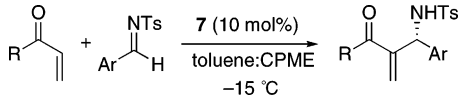


Figure 6. BINOL derivatives.

Sasai and co-workers developed bifunctional BINOL-derived organocatalyst 7 and the aza Morita−Baylis−Hillman reaction (Table 2).[60] While the 3-pyridyl moiety

Table 2. Aza Morita−Baylis−Hillman Reaction

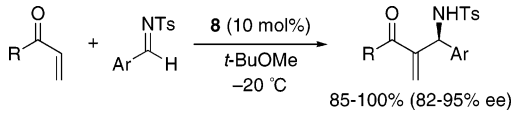


entry	R	Ar	yield (%)	ee (%)
1	Me	Ph	93	87
2	Me	*p*-ClC_6H_4	96	93
3	Me	*p*-BrC_6H_4	93	94
4	Me	2-naphthyl	94	91
5	H	*p*-$NO_2C_6H_4$	95	94

functioned as a Lewis-basic site, the binaphthol moiety worked as a Brønsted-acidic site. It should be noted that introduction of an *N*-isopropyl-*N*-3-pyridylaminomethyl moiety at the 3-position is essential to attain excellent enantioselectivity.

They subsequently introduced a 2-diphenylphosphinophenyl group at the 3-position and successfully utilized 8 as a catalyst for the aza Morita−Baylis−Hillman reaction (Scheme 19).[61]

Scheme 19



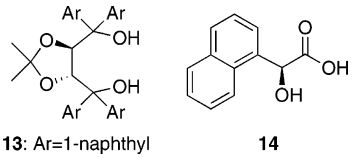
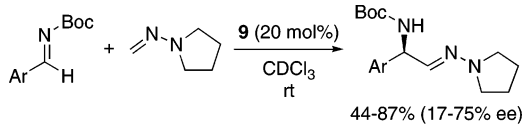


Figure 7.

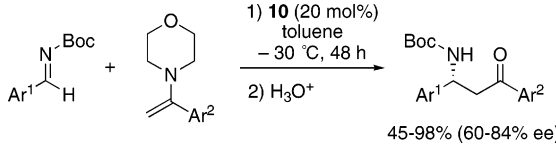
Dixon and co-workers reported that tetrol 9 catalyzed the addition reaction of methyleneaminopyrrolidine to imines, giving rise to α-aminohydrazone in 17−75% ee (Scheme 20).[62]

Scheme 20



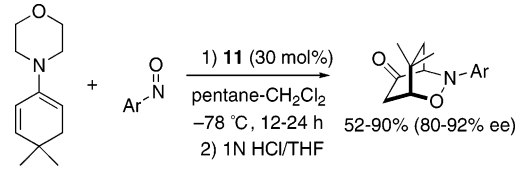
Use of enamine as nucleophile resulted in the enamine Mannich reaction in which diol 10 showed high catalytic activity (Scheme 21).[63]

Scheme 21



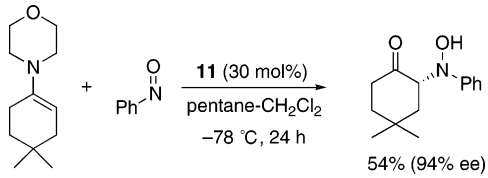
Yamamoto and co-workers reported the nitroso Diels−Alder reaction of diene with nitrosobenzene catalyzed by binaphthol derivative **11** to furnish bicyclo ketones with excellent enantioselectivities (Scheme 22).[64] Interestingly, use

Scheme 22



of morpholino-4,4-dimethylcyclohexene resulted in α-amination with excellent enantioselectivity (Scheme 23). This

Scheme 23

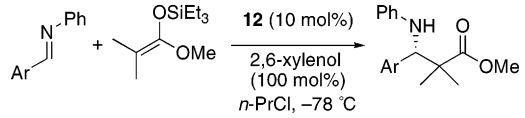


suggests the involvement of a sequential process, namely, the *N*-nitroso aldol reaction, followed by Michael addition.

Ishihara and co-workers designed Brønsted-acid-assisted chiral Brønsted-acid catalyst **12** bearing a bis(triflyl)methyl group.[65] The enantioselective Mannich-type reaction of a ketene silyl acetal with aldimines catalyzed by **12** in the presence of a stoichiometric amount of an achiral proton source gave (*S*)-*β*-amino esters in high yields with good enantiomeric excesses (Table 3).

Yamamoto and co-workers reported that an enamine reacted with nitrosobenzene by means of **13** (Figure 7) to furnish an *N*-nitroso aldol product. In contrast, use of glycolic

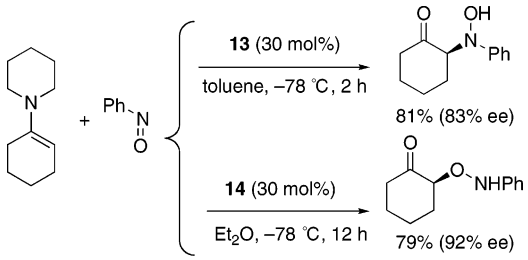
Table 3. Mannich-type Reaction



entry	Ar	yield (%)	ee (%)
1	Ph	91	69
2	p-MeC_6H_4	91	62
3	p-$CF_3C_6H_4$	99	77
4	p-FC_6H_4	89	72

acid derivative **14** gave an *O*-nitroso aldol product with high enantioselectivity (Scheme 24).[66]

Scheme 24



3.3. Amidinium Salts

Johnston and co-workers developed an ammonium salt **15** (Figure 8), which was derived from cyclohexane diamine,

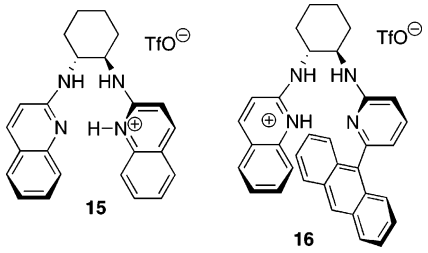
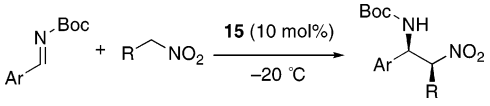


Figure 8.

and successfully utilized it as a catalyst for the aza Henry reaction (Table 4).[67] Using the Perrin titration method,[68] they

Table 4. Aza Henry Reaction

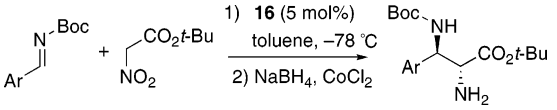


entry	Ar	R	yield (%)	dr	ee (%)
1	Ph	H	57		60
2	p-$NO_2C_6H_4$	H	61		82
3	m-$NO_2C_6H_4$	H	65		95
4	m-$NO_2C_6H_4$	Me	51	11:1	89
5	p-$NO_2C_6H_4$	Me	60	7:1	90

estimated the pK_a value of the ammonium salt to be 5.78.

They subsequently reported that **16** is an effective catalyst for addition of a nitroacetic acid derivative to aldimines, giving rise to α,β-diamino carboxylic acid derivatives with high diastereoselectivity and excellent enantioselectivity after reduction (Table 5).[69] This method is an alternative to the chiral phase-transfer-catalyzed enantioselective glycine Schiff base alkylation developed by O'Donnell and co-workers.[70]

Table 5. Aza Henry Reaction

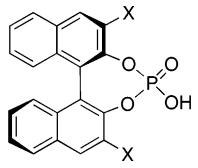


entry	Ar	yield (%)	dr	ee (%)
1	p-ClC_6H_4	88	5:1	87
2	p-FC_6H_4	81	7:1	93
3	p-MeC_6H_4	81	6:1	94
4	p-$MeO_2CC_6H_4$	84	8:1	91
5	2-naphthyl	80	11:1	94

3.4. Phosphoric Acids

3.4.1. Introduction

Chiral cyclic phosphoric acid diester **17a** (Figure 9),



17a: X=H
17b: X=Ph
17c: X=4-$NO_2C_6H_4$
17d: X=4-β-naph-C_6H_4
17e: X=4-ClC_6H_4
17f: X=3,5-$(CF_3)_2C_6H_3$
17g: X=3,5-dimesitylphenyl
17h: X=1-naphthyl
17i: X=2,4,6-$(i\text{-}Pr)_3C_6H_2$
17j: X=9-anthryl
17k: X=9-phenanthryl
17l: X=biphenyl
17m: X=2-naphthyl
17n: X=$SiPh_3$

Figure 9. Chiral cyclic phosphoric acid diesters.

derived from (*R*)-BINOL, is conventionally employed as a chiral resolving agent.[71] Inanaga and co-workers employed its lanthanide salt as a catalyst for the hetero Diels−Alder reaction.[72] The hetero Diels−Alder reaction of Danishefsky's diene with aldehyde proceeded in a highly enantioselective manner.

In 2004, our group reported that chiral phosphoric acid **17c** exhibited excellent catalytic activity as a chiral Brønsted acid. Terada subsequently reported its catalytic activity independently. After those findings, chiral phosphoric acids were acknowledged as novel chiral catalysts[73] and attracted the attention of synthetic organic chemists. It was found that **17** are bifunctional catalysts[74] bearing both Brønsted-acidic site and Lewis-basic site and the 3,3′-substituents play a crucial role in attaining excellent enantioselectivity (vide infra) (Figure 10).

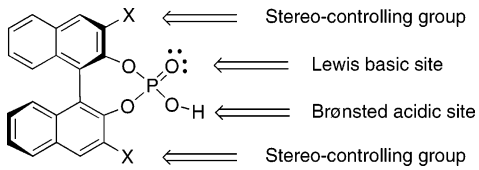


Figure 10. Functional chiral Brønsted acid.

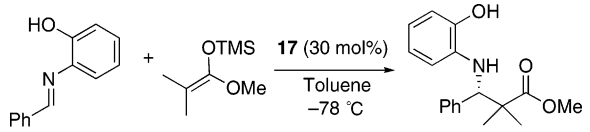
3.4.2. Nucleophilic Addition to Aldimines

We designed phosphoric acids **17** as chiral catalysts in view of the following three points. (1) Use of a readily available chiral source: (*R*)-BINOL was selected as the chiral source. (2) Suitable acidity to promote the reaction: phosphate is a candidate because the pK_a of $(EtO)_2P(O)OH$ is 1.3,[75] which is similar to HBF_4 (−0.44).[76] (3) Cyclic structure to attain high asymmetric induction: a cyclic phosphoric acid

diester **17**, bearing a BINOL scaffold, was selected as a chiral Brønsted acid.

The appropriate choice of the substituents at the 3,3′-position is crucial for realization of high enantioselectivity. For example, **17a** gave racemic compounds in the Mannich-type reaction of ketene silyl acetal with aldimines, and introduction of phenyl groups at the 3,3′-position had a beneficial effect, yielding the β-amino ester in 27% ee. Use of phosphoric acid **17c**, bearing 4-nitrophenyl groups at the 3,3′-position, gave the best result, and the corresponding β-amino ester was obtained in 87% ee (Scheme 25).

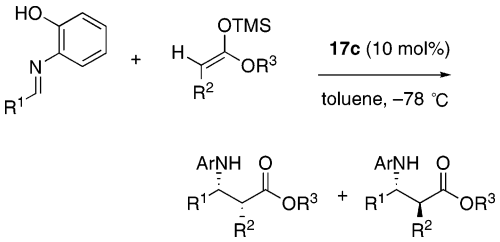
Scheme 25



17a: 57%, 0% ee
17b: 100%, 27% ee
17c: 96%, 87% ee

Phosphoric acid **17c** is effective as a catalyst for a number of aldimines and ketene silyl acetals (Table 6).[77] The

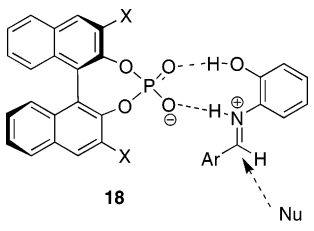
Table 6. Enantioselective Mannich-type Reaction



entry	R^1	R^2	R^3	yield (%)	*syn*/*anti*	ee (%)
1	Ph	Me	Et	100	87/13	96
2	*p*-$MeOC_6H_4$	Me	Et	100	92/8	88
3	2-thienyl	Me	Et	81	94:6	88
4	Ph	$PhCH_2$	Et	100	93/7	91
5	Ph	Ph_3SiO	Me	79	100/0	91
6	PhCH═CH	Me	Et	91	95/5	90

Mannich-type reaction exhibited high syn selectivity, and the enantioselectivity of the syn isomer was as high as 96%.

Use of aldimines derived from *o*-hydroxyaniline is essential to realize excellent enantioselectivity. On the basis of experimental results and density functional theory calculations (BHandHLYP/6-31G*), the present reaction proceeds via a dicoordination pathway through nine-membered zwitterionic cyclic transition-state **18** consisting of the aldimine and the phosphoric acid (Figure 11). The *re*-facial selectivity



18

Figure 11. Proposed nine-membered zwitterionic cyclic transition-state model of the phosphoric acid and aldimine.

was well rationalized theoretically. The nine-membered cyclic structure and the aromatic stacking interaction between the 4-nitrophenyl group and the *N*-aryl group would fix the geometry of aldimine on the transition state, and the *si*-facial attacking transition state is less favored due to the steric hindrance of the 3,3′-aryl substituents. The transition-state model calculated using a biphenol-derived phosphoric acid is shown (Figure 12).[78]

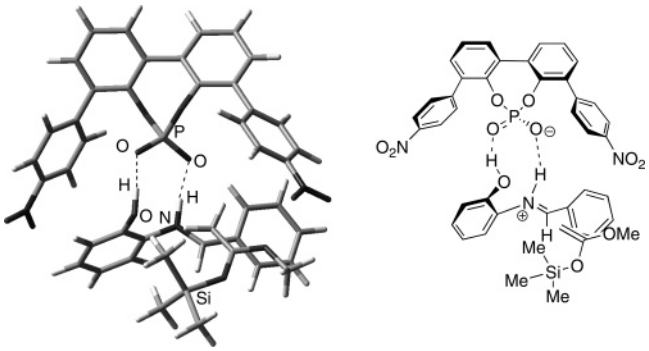
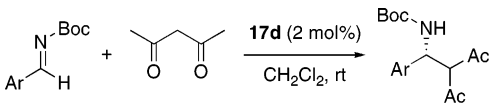


Figure 12. Zwitterionic cyclic transition state for the Mannich-type reaction.

Terada and co-workers independently found that chiral phosphoric acid **17d** catalyzed the Mannich reaction of 2,4-pentandione with aldimines, furnishing the corresponding adducts with excellent enantioselectivities (Table 7).[79]

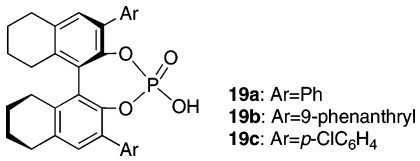
Table 7. Direct Mannich Reaction



entry	Ar	yield (%)	ee (%)
1	Ph	99	95
2	*p*-MeC_6H_4	98	94
3	*p*-BrC_6H_4	96	98
4	*p*-FC_6H_4	94	96
5	*o*-MeC_6H_4	94	93
6	1-naphthyl	99	92

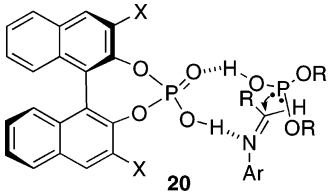
Gridnev and Terada studied a complex, derived from **17d** and *N*-Boc imine, by computational and NMR analyses, thereby rationalizing the origin of the enantioselectivity.[80]

The three-component direct Mannich reaction was reported recently, wherein H_8-BINOL derivative **19a** was employed (Figure 13).[81] Cyclohexanone derivatives turned out to be good substrates (Table 8).



19a: Ar=Ph
19b: Ar=9-phenanthryl
19c: Ar=*p*-ClC_6H_4

Figure 13.



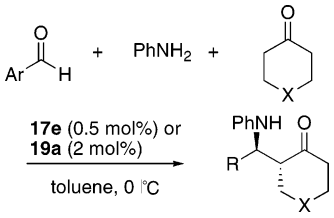
20

Figure 14. Proposed nine-membered transition state.

Hydrophosphonylation of aldimine with dialkyl phosphite proceeded by means of 10 mol % of **17f** to give α-amino-phosphonates in a highly enantioselective manner (Table 9).[82]

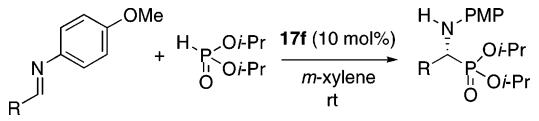
We proposed nine-membered transition-state **20** (Figure 14) wherein phosphate played two roles: (1) the phosphoric

Table 8. Three-Component Mannich Reaction



entry	X	Ar	cat.	yield (%)	dr	ee (%)
1	CH_2	*p*-$CF_3C_6H_4$	**17e**	90	72/23	94
2	CH_2	*p*-NCC_6H_4	**17e**	92	86/14	91
3	CH_2	*p*-FC_6H_4	**17e**	67	81/19	95
4	O	*p*-$O_2NC_6H_4$	**17e**	94	92/8	90
5	BocN	*p*-$O_2NC_6H_4$	**17e**	99	80/20	91
6	S	*p*-$O_2NC_6H_4$	**19a**	97	92/8	95
7	S	*p*-$CF_3C_6H_4$	**19a**	82	92/8	95

Table 9. Enantioselective Hydrophosphonylation

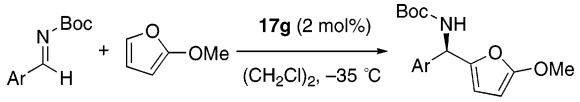


entry	R	yield (%)	ee (%)
1	Ph	100	55
2	*o*-MeC_6H_4	90	69
3	*p*-$BrC_6H_4CH{=}CH$	88	86
4	*p*-$O_2NC_6H_4CH{=}CH$	92	88
5	*p*-$CF_3C_6H_4CH{=}CH$	86	90

acid hydrogen activated the aldimine as a Brønsted acid, and (2) the phosphoryl oxygen activated the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base, thereby promoting *re* facial attack to the aldimine and increasing the enantioselectivity due to the proximity effect.

Terada and co-workers reported the aza Friedel−Crafts alkylation of furan to aldimines by means of 2 mol % of **17g** (Table 10).[83]

Table 10. Aza Friedel−Crafts Alkylation

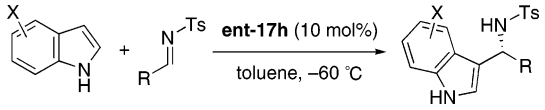


entry	R	yield (%)	ee (%)
1	Ph	87	97
2	*p*-MeC_6H_4	96	97
3	*p*-ClC_6H_4	88	97
4	*p*-FC_6H_4	82	97
5	2-naphthyl	93	96
6	2-furyl	94	86

You and co-workers demonstrated that indoles are also suitable nucleophiles for addition to aldimines catalyzed by *ent*-**17h** (Table 11).[84] High yields and excellent ee's were achieved for a wide range of aromatic aldimines.

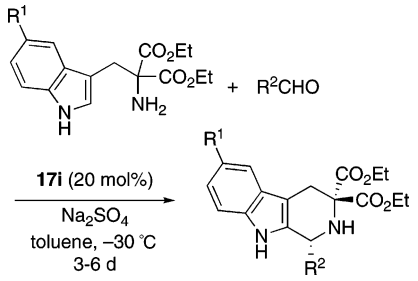
The Pictet−Spengler reaction is important for preparation of tetrahydro-*β*-carbolines and tetrahydroquinolines. List and co-workers applied the phosphoric acid catalysis to the Pictet−Spengler reaction starting from geminally disubstituted tryptamines (Table 12).[85,86] The presence of the bis(ethoxycarbonyl) group facilitated the cyclization reactions by virtue of the Thorpe−Ingold effect. Aliphatic as well as aromatic aldehydes turned out to be good substrates.

Table 11. Addition of Indole to Aldimines



entry	R	Ar	yield (%)	ee (%)
1	H	Ph	83	98
2	5-Me	Ph	89	99
3	H	*p*-MeC_6H_4	93	99
4	H	*p*-ClC_6H_4	91	94
5	H	*c*-C_6H_{11}	56	58

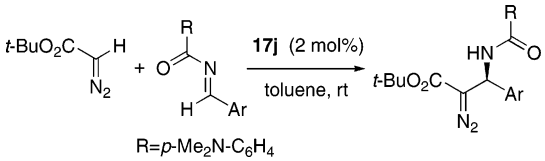
Table 12. Pictet−Spengler Reaction



entry	R^1	R^2	yield (%)	ee (%)
1	OMe	Et	96	90
2	OMe	*i*-Pr	85	81
3	OMe	*c*-C_6H_{11}	64	94
4	OMe	*p*-$NO_2C_6H_4$	98	96
5	H	*p*-NCC_6H_4	40	89

Phosphoric acid **17j**, bearing the 9-anthryl group, catalyzed the direct alkylation of aldimines with α-diazo ester to furnish *β*-amino-α-diazoester with excellent enantioselectivity (Table 13).[87] Diazoacetate is commonly employed in aziridine ring

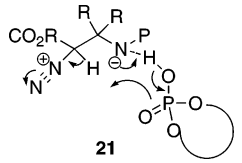
Table 13. Direct Alkylation of α-Diazo Ester



entry	Ar	yield (%)	ee (%)
1	Ph	84	97
2	*p*-FC_6H_4	74	97
3	*p*-FC_6H_4	71	97
4	*p*-MeC_6H_4	74	97
5	*m*-FC_6H_4	84	93
6		75	95

formation reactions (aza Darzens reaction) under Lewis-acidic[88] and Brønsted-acidic[38] conditions.

The addition reaction is proposed to proceed via **21** (Figure 15), wherein phosphoryl oxygen worked as a Lewis base.



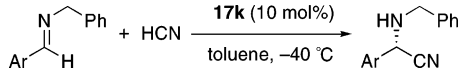
21

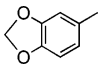
Figure 15. Proposed transition-state model.

Intramolecular deprotonation by phosphoryl oxygen may be responsible for the exclusive alkylation by suppressing the aziridine ring formation.

Rueping and co-workers reported the Strecker reaction catalyzed by **17k** (Table 14).[89] They proposed a transition-

Table 14. Strecker Reaction

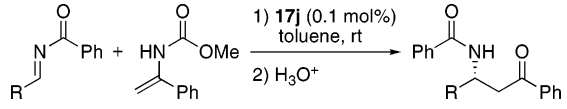


entry	Ar	yield (%)	ee (%)
1	*p*-$CF_3C_6H_4$	75	97
2	1-naphthyl	85	99
3		88	93
4	2-thienyl	77	95
5	2-furyl	84	89

state model based on the X-ray crystal structure of **17k** and optimized a complex derived from **17k** and an imine.

Enecarbamate[90] turned out to be an efficient nucleophile in the phosphoric acid-catalyzed aza ene-type addition to aldimines. It is noted that a concentration as low as 0.1 mol % of catalyst **17j** worked well to afford the adducts with excellent enantioselectivities (Table 15).[91]

Table 15. Addition of Enecarbamate



entry	R	yield (%)	ee (%)
1	Ph	82	95
2	*p*-MeC_6H_4	90	95
3	*p*-BrC_6H_4	89	95
4	*p*-NCC_6H_4	97	98
5	2-naphthyl	91	95
6	PhCH=CH	81	89

Terada and co-workers subsequently employed the enecarbamate as a precursor of iminium salt, which was trapped by indole (Table 16).[92] The phosphoric acid activated the electron-rich alkene in place of imine to give 1-indolyl-1-alkylamine derivatives having pharmaceutical and biological importance with excellent enantioselectivity.

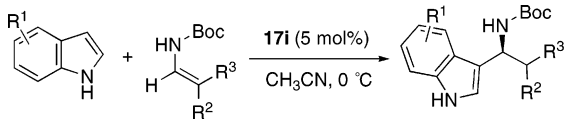
Rueping and co-workers recently reported the imino–azaenamine reaction catalyzed by partially hydrogenated phosphoric acid **19b** (Table 17).[93]

3.4.3. Aza Diels–Alder Reactions

We found that Danishefsky's diene[94] underwent the aza Diels–Alder reaction with aldimine in the presence of phosphoric acid **17i** to give cycloadducts (Table 18).[95] Interestingly, addition of acetic acid significantly improved both the chemical yield and enantioselectivity.

Brassard's diene[96] is more reactive than Danishefsky's diene. Although the diastereoselective aza Diels–Alder reaction of Brassard's diene with aldimines was already reported,[97] the catalyzed enantioselective version of the reaction has not been realized yet. Our group disclosed that a phosphoric acid **17j**, bearing a 9-anthryl group at the 3,3′-position, is effective for the aza Diels–Alder reaction. Interestingly, use of **22** (Figure 16), a pyridinium salt of **17j**, improved the chemical yield. Supposedly, use of less acidic pyridinium salt **22** suppressed decomposition of Brassard's diene in the reaction medium. Aldimines derived from aliphatic aldehydes as well as aromatic aldehydes worked

Table 16. Friedel–Crafts-type Reaction



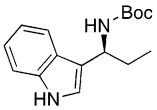
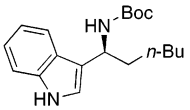
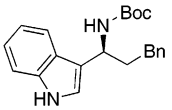
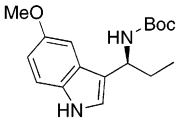
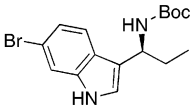
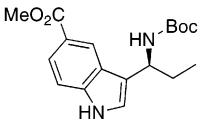
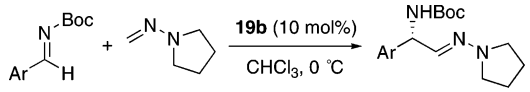
entry	product	yield(%)	ee(%)
1		87	94
2		98	94
3		82	93
4		90	90
5		78	96
6		86	93

Table 17. Imino–Azaenamine Reaction



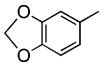
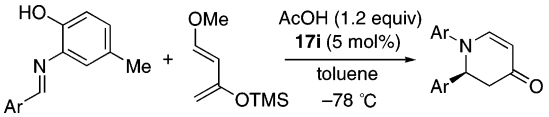
entry	Ar	yield (%)	ee (%)
1	Ph	73	74
2		81	90
3	*o*-BrC_6H_4	82	85
4	*o*-$CF_3C_6H_4$	48	83
5	*p*-ClC_6H_4	76	86

Table 18. Aza Diels–Alder Reaction



L	Ar	yield (%)	ee (%)
1	Ph	99	80
2	*o*-BrC_6H_4	86	84
3	*o*-BrC_6H_4	quant.	84
4	*p*-ClC_6H_4	82	81
5	*o*-$CF_3C_6H_4$	96	80
6	2-naphthyl	quant.	91

well to give the corresponding cycloadducts after acid treatment with excellent enantioselectivity (Table 19).[98]

The reverse electron-demand aza Diels–Alder reaction of electron-rich alkene with 2-aza diene was catalyzed by **17j** to give tetrahydroquinoline derivatives in favor of the cis

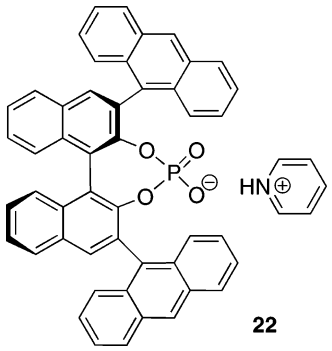
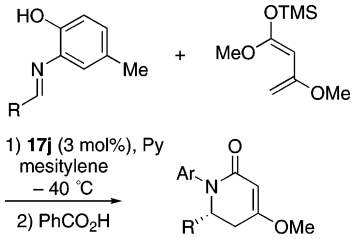


Figure 16.

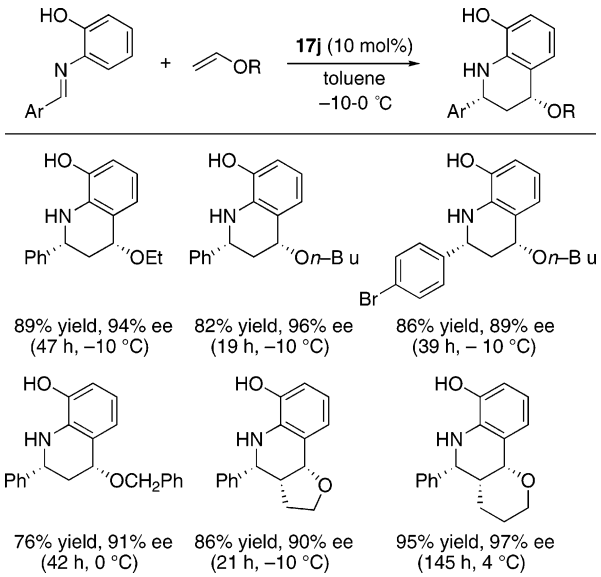
Table 19. Aza Diels−Alder Reaction



entry	R	yield (%)	ee (%)
1	Ph	87	94
2	*o*-BrC_6H_4	86	96
3	*p*-$MeOC_6H_4$	84	99
4	2-furyl	63	97
5	2-naphthyl	91	97
6	PhCH=CH	64	98
7	*c*-C_6H_{11}	69	99
8	*i*-Pr	65	93

isomer with excellent enantioselectivities (Table 20).[99] Cyclic

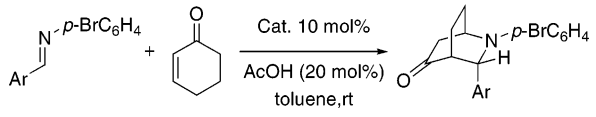
Table 20. Reverse Electron-Demand Aza Diels−Alder Reaction



enol ethers as well as acyclic enol ether turned out to be excellent substrates.

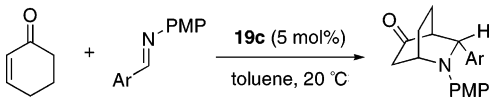
The aza Diels−Alder reaction of aldimine with cyclohexenone was independently developed by Rueping[100] and Gong.[101] While Rueping employed **17l** and **17m** in combination with acetic acid (Table 21), Gong used H_8-BINOL-derived phosphoric acid **19c** bearing *p*-ClC_6H_4 groups at the 3,3′-positions (Table 22). They proposed that cyclohexenone

Table 21. Aza Diels−Alder Reaction of Cyclohexenone with Aldimines



		cat. = **17 m**			cat. = **17l**		
entry	Ar	yield (%)	exo/endo	ee (%)	exo/endo	yield (%)	ee (%)
1	Ph	62	1:4	84	1:4	71	86
2	2-thienyl	63	1:4	86	1:4	70	88
3	9-pyrenyl	65	1:5	88	1:8	67	86
4	2,3-$(MeO)_2C_6H_3$	76	1:9	86	1:8	84	86
5	*o*-FC_6H_4	60	1:4	84	1:4	74	88

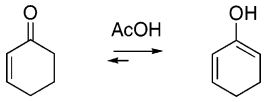
Table 22. Aza Diels−Alder Reaction of Cyclohexenone with Aldimines



entry	Ar	yield (%)	exo/endo	ee (%)
1	Ph	76	84/16	87
2	*p*-ClC_6H_4	82	82/18	85
3	*p*-FC_6H_4	72	80/20	85
4	*m*-BrC_6H_4	79	81/19	87
5	*p*-MeC_6H_4	81	83/17	83
6	*p*-NCC_6H_4	70	83/17	76

is equilibrated to the enol form by acetic acid (Scheme 26),

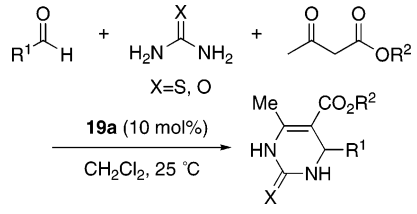
Scheme 26



thus promoting the aza Diels−Alder reaction to proceed (Figure 16).

Although the Biginelli reaction is a useful multicomponent reaction, providing ready access to multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones, the catalyzed enantioselective version of the Biginelli reaction has been little explored.[102] The highly enantioselective Biginelli reaction catalyzed by **19a** was reported by Gong and co-workers.[103] A range of 3,4-dihydropyrimidin-2-(1*H*)-ones were obtained with excellent enantioselectivities (Table 23).

Table 23. Biginelli Reaction



entry	R^1	X	R^2	yield (%)	ee (%)
1	3,5-$Br_2C_6H_3$	S	Et	66	96
2	3,5-$(CF_3)_2C_6H_3$	S	Et	56	97
3	*c*-C_6H_{11}	S	Et	40	92
4	PhCH=CH	S	Et	44	88
5	3,5-$Br_2C_6H_3$	S	Me	51	96
6	3,5-$Br_2C_6H_3$	O	Et	51	97

3.4.4. Transfer Hydrogenations

Although chemical hydrogenations normally require metal catalysts or use of stoichiometric amounts of metal hydrides, living organisms typically employ organic cofactors such as nicotinamide adenine dinucleoside (NADH) in combination with metalloenzymes.[104] The organo-catalyzed transfer hydrogenation[105] and reductive Michael reaction,[106] both of which employ Hantzsch ester **23a** as a model of NADH, were reported quite recently (Figure 17). Three groups

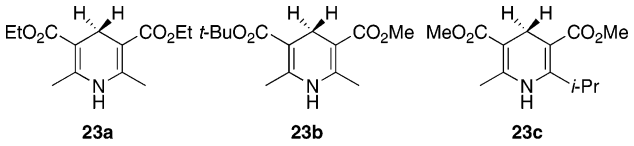
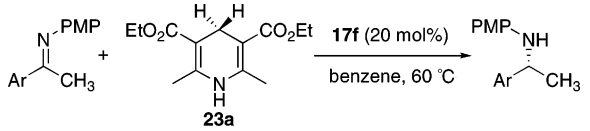


Figure 17. Hantzsch esters.

independently reported the enantioselective reduction of imines catalyzed by phosphoric acid as Brønsted acid. Rueping and co-workers employed 20 mol % of **17f**, bearing 3,5-$(CF_3)_2C_6H_3$ groups at the 3,3′-positions, as catalyst (Table 24),[107] and List and co-workers used 1 mol % of *ent*-**17i**,

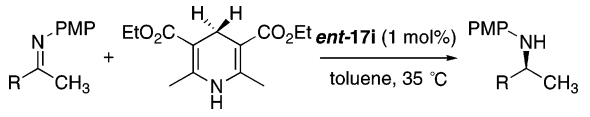
Table 24. Transfer Hydrogenation Reaction



entry	Ar	yield (%)	ee (%)
1	Ph	76	74
2	2-naphthyl	82	70
3	*o*-FC_6H_4	82	84
4	2,4-$(CH_3)_2C_6H_3$	91	78
5	*o*-$CF_3C_6H_4$	46	82

bearing 2,4,6-(*i*-Pr)$_3C_6H_2$ groups at the 3,3′-positions, as catalyst (Table 25).[108]

Table 25. Transfer Hydrogenation Reaction



entry	R	yield (%)	ee (%)
1	Ph	96	88
2	2-naphthyl	85	84
3	*o*-FC_6H_4	95	85
4	*o*-MeC_6H_4	91	93
5	2,4-$(CH_3)_2C_6H_3$	88	92
6	*i*-Pr	80	90

Rueping proposed the transition state of the transfer hydrogenation reaction based on the X-ray structure of the catalyst.

MacMillan and co-workers found that **17n** (Table 26), bearing Ph_3Si groups at the 3,3′-positions, is the catalyst of choice for the reductive amination reaction. The three-component transfer hydrogenation reaction starting from aldehydes, amine, and Hantzsch ester proceeded smoothly

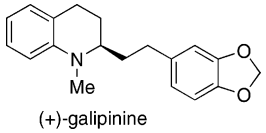
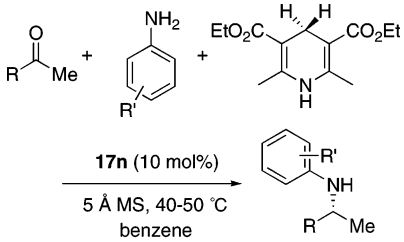


Figure 18.

Table 26. Three-Component Hydrogen Transfer Reactions



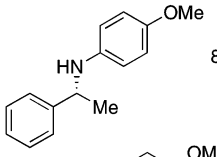
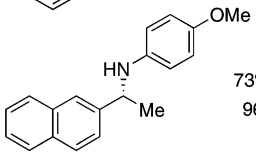
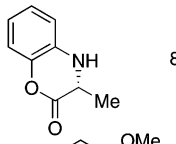
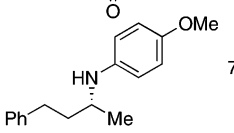
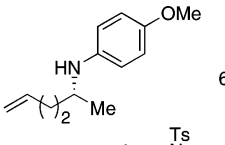
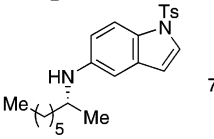
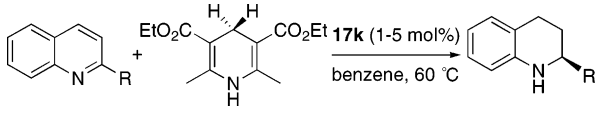
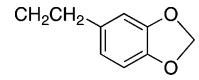
entry	product	yield, % ee
1		87% yield 94% ee
2		73% yield 96% ee
3		82% yield 97% ee
4		75% yield 94% ee
5		60% yield 90% ee
6		75% yield 90% ee

Table 27. Transfer Hydrogenation of Quinolines



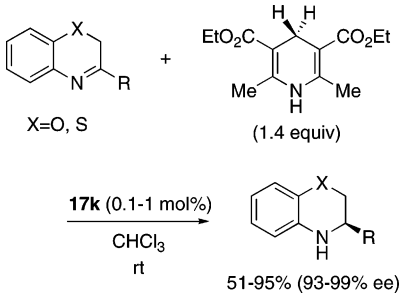
entry	R	yield (%)	ee (%)
1	Ph	92	97
2	2-naphthyl	93	99
3	*p*-$CF_3C_6H_4$	91	99
4	2-furyl	93	91
5	pentyl	88	90
6		94	91

in the presence of MS5A to give secondary amines with excellent enantioselectivities.[109] Dialkyl ketones as well as alkyl aryl ketones proved to be good substrates, and even ethyl methyl ketone was reductively aminated in 88% ee. They obtained the single-crystal X-ray structure of a catalyst-bound aryl imine, which exhibited a remarkable correlation with MM3 calculations.

Rueping and co-workers extended the chiral phosphoric acid-catalyzed transfer hydrogenation to the reduction of

quinolines (Table 27),[110] benzoxazines,[111] benzothiazines, and benzoxazinones (Scheme 27). Reduction of benzoxazines,

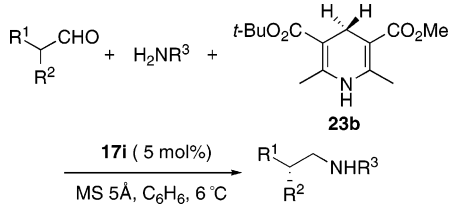
Scheme 27



in particular, is highly selective, reducing the catalyst load of **17k** to as low as 0.01 mol % without considerable loss of reactivity or selectivity. They applied the methodology to the enantioselective synthesis of biologically active tetrahydroquinoline alkaloids such as (+)-galipinine (Figure 18).

List and co-workers achieved the catalytic reductive amination of α-branched aldehydes for the first time. On treatment of α-branched aldehydes and *p*-anisidine with **23b** as a hydrogen source in the presence of 5 mol % of **17i**, *β*-substituted amines were obtained with high chemical yields with good to excellent enantioselectivities by dynamic kinetic resolution (Table 28).[112]

Table 28. Reductive Amination by Dynamic Kinetic Resolution



entry	R^1	R^2	R^3	yield (%)	ee (%)
1	Ph	Me	PMP	87	96
2	1-naphthyl	Me	PMP	85	98
3	2-thienyl	Me	PMP	49	88
4	*tert*-butyl	Me	PMP	77	80
5	Ph	Et	PMP	92	98
6	Ph	Me	Ph	78	94

3.4.5. Novel Phosphoric Acids

Several novel phosphoric acids have been reported (Figure 19).

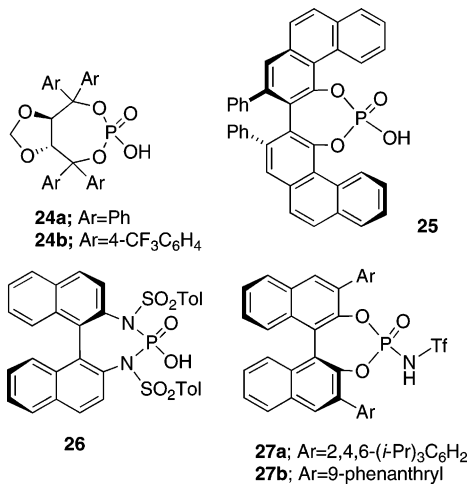
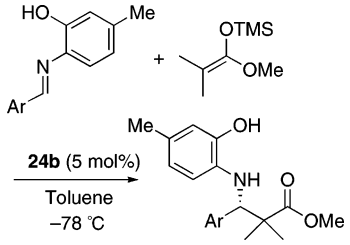


Figure 19.

TADDOL-based phosphoric acid diesters **24** were synthesized and subjected to the Mannich-type reaction. Although **24a** did not show catalytic activity, its *p*-$CF_3C_6H_4$ analogue **24b** exhibited high catalytic activity and the Mannich-type reaction proceeded smoothly to give *β*-amino esters with high enantioselectivity (Table 29).[113]

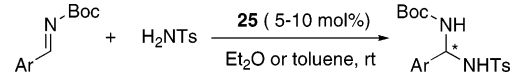
Table 29. Mannich-type Reaction



entry	Ar	yield (%)	ee (%)
1	Ph	100	89
2	*p*-FC_6H_4	95	92
3	*p*-$MeOC_6H_4$	85	89
4	*p*-MeC_6H_4	96	92

Antilla and co-workers synthesized a novel phosphoric acid derivative **25**, starting from (*S*)-VAPOL,[114] and demonstrated its catalytic activity in the addition of sulfonamide to aldimines to produce protected aminals, which have been incorporated into peptide chains as retro-inverso peptide mimics (Table 30).[115]

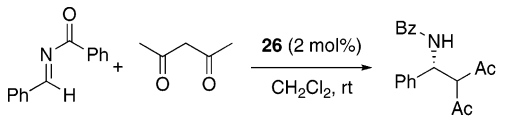
Table 30. Formation of Aminals by Addition of Sulfonamide to Aldimines



entry	Ar	yield (%)	ee (%)
1	Ph	95	94
2	*p*-ClC_6H_4	88	94
3	*p*-BrC_6H_4	96	92
4	*p*-$CF_3C_6H_4$	99	99
5	*p*-$MeOC_6H_4$	92	90
6	2-thienyl	94	87

Phosphorodiamidic acid derivative **26** has been developed as a Brønsted acid for the direct Mannich-type reactions (Scheme 28).[116]

Scheme 28



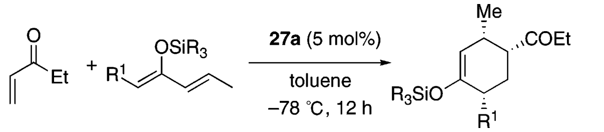
Yamamoto and co-workers designed a stronger chiral Brønsted acid in an effort to expand the substrate scope for the chiral Brønsted-acid-catalyzed reactions. *N*-Triflyl phosphoramide **27a**, bearing a BINOL backbone, catalyzed the Diels−Alder reaction of α,*β*-unsaturated ketone with electron-rich diene to give cyclohexene derivatives with high enantioselectivities (Table 31).[117]

Rueping and co-workers reported the Nazarov cyclization reaction catalyzed by **27b** (Table 32).[118] This is the first example of an organocatalytic electrocyclization reaction.

3.4.6. Miscellaneous

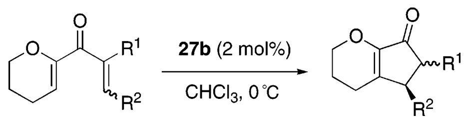
Although the reactions discussed below are not chiral Brønsted-acid-catalyzed reactions, we included them in this

Table 31. Diels–Alder Reaction



entry	R_3Si	R^1	yield (%)	ee (%)
1	TBS	Me	43	92
2	TIPS	Me	95	92
3	TIPS	H	43	88
4	TIPS	$(4\text{-TBSOC}_6H_4)CH_2$	99	92
5	TIPS	$BzOCH_2CH_2$	99	91

Table 32. Nazarov Cyclization

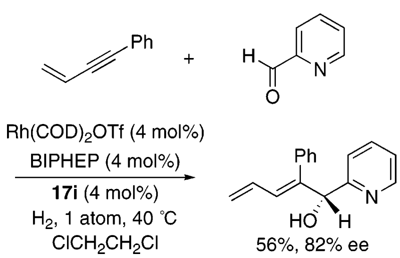


entry	R^1	R^2	yield (%)	*cis*/*trans*	ee (%)
1	Me	Ph	88	6:1	87
2	pentyl	Ph	78	2.3:1	91
3	Et	2-naphthyl	61	4.3:1	88
4	propyl	Ph	85	3.2:1	93
6	propyl	p-BrC_6H_4	72	3.7:1	92

review because they provide important information for the future development of the chiral Brønsted-acid catalysis.

Krische and co-worker reported the enantioselective reductive coupling of 1,3-enynes to heteroaromatic aldehydes and ketones by rhodium-catalyzed asymmetric hydrogenation, wherein Brønsted-acid cocatalyst enhanced both reaction rate and conversion. In order to elucidate the mechanism, they employed chiral phosphoric acid **17i** as a cocatalyst, and high enantioselectivity was observed (Scheme 29).[119]

Scheme 29



List and co-workers reported the counteranion-directed transfer hydrogenation reaction by means of **28a** (Figure 20).[120] The reduction proceeded via an iminium salt intermediate, wherein phosphate anion effectively shielded one of the enaniofaces of the iminium salt (Table 33).They

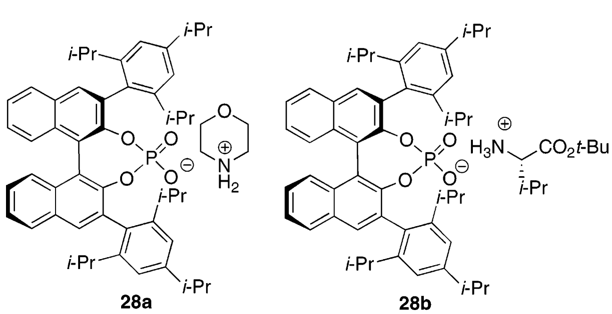
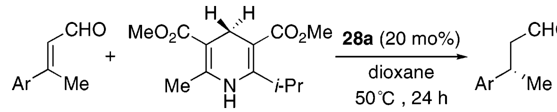


Figure 20. Counteranion-directed catalysts.

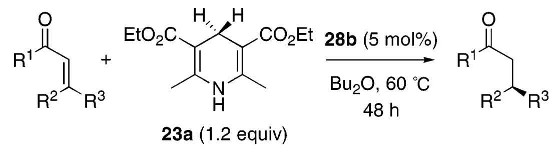
Table 33. Counteranion-Directed Transfer Hydrogenation

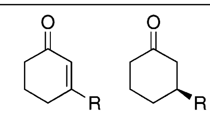
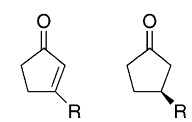


entry	Ar	yield (%)	ee (%)
1	p-$CH_3C_6H_4$	87	96
2	p-NCC_6H_4	84	98
3	p-$O_2NC_6H_4$	90	98
4	p-BrC_6H_4	67	96
6	2-naphthyl	72	99

subsequently reported that a valine ester phosphate salt **28b** was an active catalyst for the reaction of a variety of α,β-unsaturated ketones with Hantzsch ester **23a** to give saturated ketones in excellent enantioselectivities (Table 34).[121]

Table 34. Transfer Hydrogenation with Valine Phosphate



entry	enone	product	yield(%)	ee(%)
				
1	R=Me		99	94
2	R=Et		98	96
3	R=*i*-Pr		94	98
4	R=Ph		99	84
				
5	R=Me		78	98
6	R=Et		71	96

4. Summary and Outlook

We discussed Brønsted-acid-catalyzed reactions starting from achiral reactions and ending with catalyzed enantioselective reactions. Spectacular advancement has been made in the area of "stronger Brønsted-acid catalysis". The scope of the substrates is expanding at an unprecedented pace, and there is no doubt that more and more useful synthetic reactions will be developed in the near future. Mechanistic studies of chiral Brønsted-acid catalysis are required to expand the scope and develop even more efficient and novel types of chiral Brønsted-acid catalysis. Although chiral Brønsted-acid catalysis is, thus far, restricted to academic synthesis, industrial applications are expected from economic and environmental points of view. We believe that chiral Brønsted-acid catalysts and metal-oriented chiral catalysts will complement each other and make significant contributions to synthetic organic chemistry.

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